22. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is transcribed by an adenovirus VA1 RNA promoter system.

23. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is a chimeric adenovirus VA1 RNA.

24. (Amended) The RNA molecule of claim 1, wherein said intramolecular stem is separated from said desired therapeutic RNA portion by spacer sequence.

REMARKS

Claim Amendments

Claims 1-25 are currently pending. Claims 1-24 have been amended to correct matters of form and to more particularly point out and distinctly claim the present invention. Support for the amendments can be found throughout the specification. Accordingly, no new matter has been added by way of these amendments. These amendments are made without prejudice. Applicant reserves the right to pursue the subject matter of the originally filed claims in this or in any other appropriate patent application. A marked-up copy of the amended claims appears in Appendix A.

Specification

Applicant has submitted a new abstract of the disclosure on a separate sheet, in accordance with 37 C.F.R. § 1.52(b)(4), and respectfully requests that it be included with the present application. The abstract contains no new matter.

THE OFFICE ACTION

The November 05, 2001 Office Action set forth the following rejections

1. Claims 1-17 and 20-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-21 of U.S. Patent No. 6,146,886.
2. Claims 1-17 and 20-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-24 of U.S. Patent No. 5,902,880.
3. Claims 6-9, 12, 13, 15-19, 24 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.
4. Claims 1-25 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with the claims.
5. Claims 1, 9-12, 15-19, 24, and 25 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Inouye (U.S. Patent No. 5,208,149).
6. Claims 1, 2, 9-19, 21, 24, and 25 are rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Noonberg et al. (U.S. Patent No. 5,624,803).

Discussion of the Double Patenting Rejections

Claims 1-17 and 20-25 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-21 of U.S. Patent No. 6,146,886. Without conceding to the merits of the present rejection, but solely in an effort to

expedite prosecution, Applicant has submitted a terminal disclaimer for these claims, rendering the rejection moot. Accordingly, Applicant respectfully requests withdrawal of the double-patenting rejection.

Claims 1-17 and 20-25 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-24 of U.S. Patent No. 5,902,880. Without conceding to the merits of the present rejection, but solely in an effort to expedite prosecution, Applicant has submitted a terminal disclaimer for these claims, rendering the rejection moot. Accordingly, Applicant respectfully requests withdrawal of the double-patenting rejection.

Discussion of the 35 U.S.C. § 112, Second Paragraph Rejection

Claims 6-9, 12, 13, 15-19, 24 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed.

In an attempt to clarify the scope of the instant claims and expedite the issuance of this application, Applicant amended the claims according to the Examiner's several suggestions. With regard to claims 6-9, 18, and 24, which are alleged to be indefinite because the metes and bounds of the term "desired RNA molecule" are unclear, Applicant has amended claims 6-9 and 24 to recite "desired therapeutic RNA portion" of the RNA molecule. In addition, Applicant respectfully points out that the term "desired RNA molecule" is defined in the specification, *inter alia*, at page 8, lines 6-11, as "any foreign RNA molecule which is useful from a therapeutic, diagnostic, or other viewpoint. Such molecules include antisense RNA molecules, decoy RNA molecules, enzymatic RNA, therapeutic editing RNA . . . and agonist and antagonist." In light of the specification as filed,

one skilled in the art would understand the metes and bounds of the term "desired RNA molecule." Applicant has amended claims 12, 13, and 15-19 to include an article as suggested by the Examiner. Applicant has also amended claim 19 to provide the proper antecedent basis, as suggested by the Examiner. In addition, Applicant has amended claim 18 to address the issues raised by the Examiner and clarify the claimed subject matter. In view of the above, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, second paragraph, rejections.

Discussion of the 35 U.S.C. § 112, First Paragraph Rejection

Claims 1-25 are rejected under 35 U.S.C. § 112, first paragraph because allegedly the specification does not reasonably provide enablement for a method of introducing an RNA molecule into a cell *in vivo* (whole organism), and because allegedly the specification does not reasonably provide enablement for a transcribed RNA molecule that comprises a therapeutic portion. This rejection is respectfully traversed.

Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, to enable claims 1-25, the specification must teach one skilled in the art how to make and use a method of introducing an RNA molecule into a cell *in vivo* and how to make and use a transcribed RNA molecule that comprises a therapeutic portion. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the application coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

Contrary to the Office's allegation, the specification provides considerable guidance to enable a skilled artisan to make and use a method of introducing an RNA molecule into a cell *in vivo*. The Office Action concedes that the specification is enabling for a method of introducing an RNA molecule into a cell *in vitro*, based on the Applicant's description and demonstration of stable gene transfer of the hammerhead ribozyme into human MT2 T cell lines (see specification at, for example, pages 11 and 17-21). In addition, the specification at, *inter alia*, page 21, line 21 to page 22, line 10 and Figure 6, teaches the stable transduction of ribozymes into a CEM cell line, resulting in the expression of active ribozyme. Moreover, other methods for the delivery of nucleic acids to cells were known in the art at the time of filing. For example, exogenous delivery methods for synthetic oligonucleotides and nucleic acid sequences contained in plasmids were known and described in Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd ed., 1989, sections 16.30-.32). In addition, Uhlmann et al. describes various methods for delivering modified oligonucleotides to cells (Uhlmann et al. (1990) Chemical Reviews 90:544). Also, the exogenous delivery of nucleic acid into eukaryotic cells using cationinc lipids was well known at the time of filing (see, e.g., Malone et al. (1989) Proc. Nat. Acad. Sci. USA 86:6077). Based on the above-described teachings of the application and known methods at the time of filing one skilled in the art would have known how to introduce an RNA molecule into a cell *in vivo*.

Despite these teachings, the Office Action alleges that the invention is not enabled because the specification does not provide any examples wherein an RNA molecule is provided to a cell *in vivo*. Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, however, does not turn on whether an example is disclosed. M.P.E.P. § 2164.02. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art

will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970); M.P.E.P. § 2164.02. Applicants submit that, based on teachings and examples relating to *in vitro* methods of RNA transfer to cells, one skilled in the art would have known how to introduce RNA into a cell *in vivo*, using the described tranfer techniques.

The Office argues that such "*in vitro* methods typically do not translate into success *in vivo*." The test, however, established by the Federal Circuit, for correlation of *in vitro* data and a claimed method of use is that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate.* M.P.E.P. § 2164.02 (emphasis added); *see In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Also, "[a] rigorous or an invariable exact correlation is not required" to enable a pharmacological invention. M.P.E.P. § 2164.02; *see Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). As further support for this position, the Federal Circuit has found that data showing the successful use of compounds as anti-tumor substances in tumor model systems were sufficient to enable the use of those compounds as anti-cancer drugs in animals. *Brana*, 34 U.S.P.Q.2d at 1436. Moreover, therapeutic inventions do not preclude "the expectation of further research and development;" for example, FDA approval is not a prerequisite for patent protection. *Brana*, 34 U.S.P.Q.2d at 1442-42.

In the present case, as discussed above, the specification clearly teaches the successful transfer of an RNA molecule to a cell in cell culture. Further, the specification demonstrates that the delivered RNA molecule is stably expressed in the target cell over a significant period of time (see, for example, pages 21-22). Moreover, at the time of filing, other cell culture studies, such as those

described in Cameron *et al.*, demonstrated the transfer, expression, and activity of catalytic RNA molecules in cell culture. Cameron et al. (1989) Proc. Nat. Acad. Sci. USA 86:9139. One of ordinary skill in the art would have recognized that appropriate cell cultures could be used as a predictive model for RNA delivery and activity *in vivo*. Thus, in the absence of any evidence that the current model does not correlate, the specification is enabled for providing an RNA molecule to a cell *in vivo*.

In addition, the instant specification provides considerable guidance to enable a skilled artisan to make and use a transcribed RNA molecule that comprises a therapeutic portion. For example, the specification, on pages 15-16, among others, teaches the use of the present invention as an antiviral therapy. Briefly, the RNA molecules and methods of the present invention can be used to express antiviral genes in cells, resulting in the establishment of immunity to viral infections. *Specification* at 15. In such a case, the present invention allows the increased accumulation of RNA molecules in the cells, thereby increasing their therapeutic usefulness. *Specification* at 15-16. In addition, the specification, at pages 19-22, among others, teaches that a RNA molecule containing a ribozyme and an intra-molecular stem of the present invention, formed by base-pairing interactions between a 3' region and 5' complementary nucleotides, results in greater accumulation in a cell than an RNA molecule containing the same ribozyme without the intra-molecular stem loop of the present invention. Further, the specification teaches that the present invention can be used with other therapeutic RNAs, including, but not limited to, ribozymes, antisense, decoy, therapeutic editing, agonist and antagonist RNAs. *Specification* at 17 and 25. These examples are merely illustrative, and are not meant to be limiting of the teachings of the specification.

Despite these teachings, the Office alleges that gene therapy methods are highly

unpredictable, and that in order to result in a therapeutic effect, the expression of the oligonucleotide must be sufficient to provide the therapeutic effect or block expression of a gene. Verma *et al.* is cited for the proposition that expression of vectors *in vivo* is often too low for therapeutic effect. Contrary to the Office's assertion, however, the specification does provide guidance for the expression of the claimed RNA molecule to provide a therapeutic effect in a cell. For example, the specification teaches throughout that using an intra-molecular stem, formed by base-pairing interactions between a 3' region and 5' complementary nucleotides, can significantly enhance the level of production of a foreign RNA; for example, see pages 18-19. In addition, the specification teaches, at pages 21, among others, that ribozymes containing an intra-molecular stem formed by base-pairing interactions between a 3' region and 5' complementary nucleotides were active when expressed in transduced cells. Also, the specification teaches at, among other places, page 22, that transduced mammalian cell lines expressed significant levels of this ribozyme, even after 3 months. These examples are merely illustrative, and are not meant to be an exhaustive listing of the teachings within the specification concerning the level of expression of an RNA molecule in a cell. Thus, a person skilled in the art to which the present invention pertains would understand that the specification teaches how to deliver a RNA molecule to a cell to provide a therapeutic effect.

Further, the Office cites Orkin, *et al.*, Anderson, and Verma *et al.* for the proposition that at the time of filing, methods for the delivery of an RNA molecule or vector to a cell and expression from said vector were thought to be highly unpredictable. In the absence of any technical reasons as to why the described methods would not work, these articles are insufficient to establish a *prima facie* case of lack of enablement, because other studies contemporaneous with these articles clearly demonstrate that RNA molecules and vectors can be delivered to cells *in vivo*, RNA molecules can

be expressed from the delivered vectors, and that RNA molecules can be active in the cells *in vivo* (*see, e.g.*, Flory *et al.* 1996, *Proc. Natl. Acad. Sci.* USA, 93, 754; Larsson *et al.*, 1994, *Nucleic Acid Res.* 22, 2242; Efrat *et al.*, 1994, *Proc. Natl. Acad. Sci.* USA, 91, 2051; Lyngstadaas *et al.*, 1995, *EMBO. J.* 14, 5224; Lieber and Kay, 1996, *J. Virol.* 70, 3153; Yamamoto *et al.*, 1996, *Int. J. Cancer,* 65, 519; Sioud, 1996, *Eur. J. Immunol.* 26, 1026; Cushman *et al.*, 1996, "Ribozyme inhibition of VEGF-mediated endothelial cell proliferation in cell culture and VEGF-induced angiogenesis in rat corneal model" Abstract in IBC USA Conferences–Angiogenesis Inhibitors; and Desjardins *et al.*, 1996, *J. Pharmacol. Exptl. Ther.* 278, 1419).

Further, the Office alleges that it would require undue trial and error experimentation to determine how to specifically deliver an RNA molecule with a therapeutic portion to a target cell in vivo. In this regard, the law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985); M.P.E.P. § 2164.01. Therefore, "[t]he test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976);); M.P.E.P. § 2164.01. As discussed above, using the teachings in the specification, one skilled in the art could make and test the RNA molecule in cell culture and biological systems that would be predictive of *in vivo* effect. Thus, even if one skilled in the art would require some experimentation to practice the present invention, the experimentation would be

merely routine, and would not constitute undue experimentation.

Finally, although FDA approval is not required to obtain patent protection for pharmaceutical inventions, it can provide further confirmation that those skilled in the art, as well as the regulatory authority, accept the therapeutic uses of RNA molecules. In the present case, this acceptance is demonstrated by the FDA approval of an Investigational New Drug application for ribozyme inhibition of various targets, including HIV (see Seachrist, *Bioworld Today*, Jan. 15, 1997, at 1), Hepatitis C (see RPI Press Release, Oct. 8, 2001, http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=742975&TICK=RZYM&STORY=/www/story/10-08-2001/0001586793&EDATE=Oct+8,+2001) and cancers, such as breast, ovarian, and colorectal cancer (see RPI Press Release, Aug. 29, 2001, http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=742975&TICK=RZYM&STORY=/www/story/08-29-2001/0001562763&EDATE=Aug+29,+2001; and RPI Press Release, June 20, 2001, http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=742975&TICK=RZYM&STORY=/www/story/06-20-2001/0001517763&EDATE=Jun+20,+2001). The therapeutic use of RNA molecules for the treatment of other diseases, in addition to those currently in clinical trials, would not require undue experimentation by those of ordinary skill in the art based on the guidance provided in the instant specification and from the work done on the wide range of targets, cell types, and diseases described above.

For the reasons set forth above, the specification satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection be withdrawn.

Discussion of the 35 U.S.C. § 102 Rejections

Claims 1, 9-12, 15-19, 24, and 25 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Inouye (U.S. Patent No. 5,208,149). Further, claims 1, 2, 9-19, 21, 24, and 25 are rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Noonberg *et al.* (U.S. Patent No. 5,624,803). These rejections are respectfully traversed.

The amended claims are directed to a transcribed non-naturally occurring RNA molecule, comprising a desired therapeutic RNA portion, wherein said molecule comprises an intra-molecular stem formed by base-pairing interactions between a 3' region and 5' complementary nucleotides in said RNA, wherein said stem comprises at least 8 base pairs, and wherein said desired therapeutic RNA portion is present between the 3' region and the 5' complementary nucleotides. Under 35 U.S.C. § 102(b), a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); M.P.E.P § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); M.P.E.P. § 2131.

Inouye does not anticipate claims 1, 9-12, 15-19, 24, and 25 because Inouye does not teach or suggest the presently claimed RNA molecule, which comprises an intra-molecular stem formed by base-pairing interactions between a 3' region and 5' complementary nucleotides in said RNA and a desired therapeutic RNA portion which is present between the 3' region and the 5' complementary nucleotides. Instead, Inouye describes non-naturally occurring RNA molecules with terminal stem-loop structures. For example, as shown in Figure 3 of Inouye, the RNA molecule is flanked by two intra-molecular stem-loop structures at its 5' end and one stem loop structure at the 3' end. The

instantly claimed invention is therefore distinct from the RNA molecules described in Inouye and, hence, Applicant respectfully requests that the 35 U.S.C. § 102(b) rejection be withdrawn.

Noonberg *et al.* ("Noonberg 1") does not anticipate claims 1, 2, 9-19, 21, 24, and 25 because the priority document of Noonberg 1, Serial No. 08/138,666 ("Noonberg 2"), does not teach or suggest a molecule comprising an intra-molecular stem formed by base-pairing interactions between a 3' region and 5' complementary nucleotides in said RNA, wherein a desired therapeutic RNA portion is present between the 3' region and the 5' complementary nucleotides. Noonberg 1 issued from a continuation-in-part application that claimed priority to Noonberg 2. Because Noonberg 1 was filed subsequent to the priority date of the present application, only disclosures found in Noonberg 2 can anticipate the present claims.

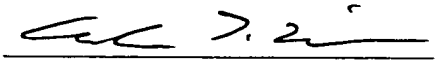
In contrast to the presently claimed molecules, Noonberg 2 describes a molecule with "self-complementary ends" where the oligonucleotide form "small double-stranded hairpin loops" (page 9, first paragraph, lines 12-14) at each end. These molecules are shown in Figure 2 as "sample transcript." The instantly claimed invention is therefore distinct from the RNA molecules described in Noonberg 2. Further, any additional disclosure in Noonberg 1, as compared to Noonberg 2, is not prior art to the present claimed invention. For example, without conceding the merits of the Office's argument, the lariat structure described in the Office Action is only found in Noonberg 1, and is not taught or suggested in Noonberg 2, the priority document, and thus cannot be cited as anticipating the present invention. Therefore, Applicant respectfully requests that the 35 U.S.C. § 102(e) rejection be withdrawn.

Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Date: February 6, 2002



Andrew W. Williams
Registration No. 48,644

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
32nd Floor
Chicago, Illinois 60606
312/913-0001 Telephone
312/913-0002 Facsimile

APPENDIX A

1. (Amended) A transcribed non-naturally [occuring] occurring RNA molecule, comprising a desired therapeutic RNA portion, wherein said molecule comprises an intramolecular stem formed by base-pairing interactions between a 3' region and 5' complementary nucleotides in said RNA, wherein said stem comprises at least 8 base pairs, and wherein said desired therapeutic RNA portion is present between the 3' region and the 5' complementary nucleotides.

2. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is transcribed by a RNA polymerase III based promoter system.

3. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is transcribed by a type 2 pol III promoter system.

4. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is a chimeric tRNA.

5. (Amended) The RNA molecule of claim 3, wherein said RNA molecule [having] has A and B boxes of a type 2 pol III promoter separated by between 0 and 300 bases.

6. (Amended) The RNA molecule of claim [3] 5, wherein said desired therapeutic RNA [molecule] portion is at the 3' end of said B box of said RNA molecule.

7. (Amended) The RNA molecule of claim [3] 5, wherein said desired therapeutic RNA [molecule] portion is in between said A and [the] said B box of said RNA molecule.

8. (Amended) The RNA molecule of claim [3] 5, wherein said desired therapeutic RNA [molecule] portion includes said B box of said RNA molecule.

9. (Amended) The RNA molecule of claim 1, wherein said desired therapeutic RNA [molecule] portion is selected from the group consisting of antisense RNA, decoy RNA,

therapeutic editing RNA, enzymatic RNA, agonist RNA and antagonist RNA.

10. (Amended) The RNA molecule of claim 1, wherein said 5' [terminus] complementary nucleotides of said RNA molecule [is] are able to base-pair with at least 12 bases of said 3' region.

11. (Amended) The RNA molecule of claim 1, wherein said 5' [terminus] complementary nucleotides of said RNA molecule [is] are able to base-pair with at least 15 bases of said 3' region.

12. (Amended) A DNA vector encoding the RNA molecule of claim 1.

13. (Amended) A RNA vector encoding the RNA molecule of claim 1.

14. (Amended) The DNA vector of claim 12 wherein the portions of the DNA vector encoding said RNA molecule function as a RNA pol III promoter.

15. (Amended) A [Cell] cell comprising the vector of claim 12.

16. (Amended) A [Cell] cell comprising the vector of claim 13.

17. (Amended) A [Cell] cell comprising the RNA of claim 1.

18. (Amended) A [Method] method to provide a desired first RNA molecule in a cell, comprising introducing [said molecule] into said cell a second RNA molecule comprising a 5' terminus, a 3' terminus, and said desired first RNA molecule, [having a] wherein said 5' terminus is able to base pair with at least 8 bases of [a] said 3' region [of said RNA molecule], and wherein said desired first RNA molecule is present between the bases of the 3' region and the 5' terminus capable of base pairing in the second RNA molecule under conditions suitable to provide the desired first RNA molecule in the cell.

19. (Amended) The method of claim [16] 18, wherein [said introducing] the

introduction of the second RNA molecule comprises providing a vector encoding said second RNA molecule.

20. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is transcribed by a RNA polymerase II promoter system.

21. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is transcribed by a U6 small nuclear RNA promoter system.

22. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is transcribed by an adenovirus VA1 RNA promoter system.

23. (Amended) The RNA molecule of claim 1, wherein said RNA molecule is a chimeric adenovirus VA1 RNA.

24. (Amended) The RNA molecule of claim 1, wherein said intramolecular stem is separated from said desired therapeutic RNA portion by spacer sequence.